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ARTICLE

An Efficient and Selective α-Monobromination of Aromatic Ketones under Ultrasonic Irradiation in Aqueous Medium

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ABSTRACT

A facile, efficient, environmentally benign protocol has been developed for rapid synthesis of α-bromoacetophenones from direct reaction of acetophenones and N-bromosuccinimide by using ultrasound waves within 15-20 min with good to excellent yields. Their formation characterized by IR, ^{1}H NMR and mass spectroscopy.

KEYWORDS

Ultrasound, α-Bromo acetophenones, Selective monobromination, PEG-400; N-Bromosuccinimide

INTRODUCTION

α-Haloketones, first obtained and described as early as the end of the 18th century [1] have been attracting increasing attention in view of their high reactivity and widely used as most important precursors for the synthesis of various classes of heterocyclic compounds *viz*. furans [2], benzofurans [3], 2-aroylbenzofurans [4], naphthofuranone [5], furocoumarins [6], azaindolizine [7], thiophene [8], 2-aminoimidazole [9].

Ultrasound waves act as a non-conventional energy source and selective, reduced reaction time and simple operation. It used in (a) organic synthesis (b) nanomaterial synthesis and (c) sonoelectrochemistry [10]. Recently, ultrasound used in organic synthesis due to it enhance reaction rates and improve yields of reactions [11,12]. In recent years, many improved methods have been reported for α-bromination by using molecular bromine or Br_2/NaH, NBS/NaH or $CuBr_2$ with hydroxy(tosyloxy)-iodo benzene or $Mg(ClO_4)_2$, from olefins using $TsNBr_2$ [13]. All these methods provides good yields but most of them have disadvantages [14-30]. In this approach instead of using toxic, corrosive and irritating bromine, we used eco-friendly N-bromo-succinimide for the selective monobromination of various substituted acetophenones in water as affordable and green solvents.

EXPERIMENTAL

All the chemicals and solvents were of AR grade and used without further purification. The completion of reactions were monitored with the help of thin layer chromatography using precoated aluminium sheets with GF254 silica gel, 0.2 mm layer thickness by E. Merck (Darmstadt, Germany). Melting

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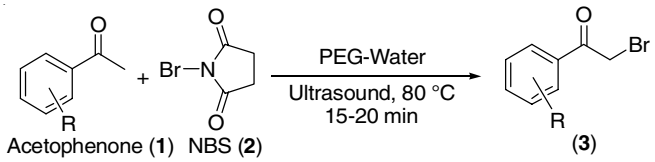
points were determined in open capillary tubes and are uncorrected. IR spectra were recorded on Shimadzu FT-IR-8400 instrument using KBr pellet method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using direct inlet probe technique. ^{1}H NMR and ^{13}C NMR was determined in DMSO-d_6 solvent on a Bruker AC 400 MHz Spectrometer. Ultrasound wave for sonochemical synthesis is generated with the help of ultrasonic instrument set-up (horn type).

General procedure for synthesis of compounds (3a-3j): A mixture of acetophenone (**1**) (1.0 eq) and N-bromosuccinimide (NBS, **2**) (1.0 eq) was added to PEG-400 and water (5 mL) with stirring. The reaction mixture was then placed under sonication using an ultrasonic horn (ACE horn, 25 kHz frequency) at 40 % amplitude for required time with the temperature of the process was maintained at 80 ºC by means of supply of water to jacketed reactor, used for the synthesis. The reaction was monitored by TLC by observing complete consumption of the reactant acetophenone. The reaction mass was extracted using dichloromethane. The dichloromethane layer was subjected to evaporation under reduced vacuum to obtain the final product (**Scheme-I**). The spectral data of synthesized compounds were consistent with previous literature report [31,32].



Scheme-I

2-Bromo-1-phenylethanone (3a): m.p. 48-49 ºC; lit. 49-51 ºC [32]; ^{1}H NMR (400 MHz, $CDCl_3$) d 4.31 (s, 2H), 7.45-7.52 (m, 2H), 7.61-7.74 (m, 1H), 7.98-7.99 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) d 30.12, 126.54, 127.16, 132.12, 133.33, 190.83. HRMS (ESI) *m/z* 197.9679, calc. for C_8H_7OBr 197.9683.

2-Bromo-1-(4-chlorophenyl)ethanone (3b): m.p. 88-89 ºC; lit. 87-89 ºC [32]; ^{1}H NMR (400 MHz, $CDCl_3$) d 4.46 (s, 2H), 7.66-7.69 (m, 2H), 7.85-7.89 (m, 2H).^{13}C NMR (125 MHz, $CDCl_3$) d 30.51, 130.57, 131.22, 132.95, 133.51, 190.22. HRMS (ESI) *m/z* 232.3786, calc. for C_8H_7OBrCl 232.3783.

2-Bromo-1-(2-bromophenyl)ethanone (3c): ^{1}H NMR (400 MHz, $CDCl_3$) d 4.48 (s, 2H), 7.35-7.38 (m, 1H),7.40-7.43 (m, 1H), 7.47-7.48 (m, 1H), 7.63-7.64 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) d 34.19, 119.32, 128.42, 129.36, 131.27, 133.44. 137.95, 193.98. HRMS (ESI) *m/z* 275.8785, calc. for $C_8H_6OBr_2$ 275.8789.

2-Bromo-1-(4-bromophenyl)ethanone (3d): ^{1}H NMR (400 MHz, $CDCl_3$) d 4.42 (s, 2H), 7.64-7.66 (m, 2H), 7.81-7.85 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) d 30.39, 129.84, 130.92, 131.95, 133.41, 190.27. HRMS (ESI) *m/z* 275.8785, calc. for $C_8H_6OBr_2$ 275.8782.

2-Bromo-1-(4-methoxyphenyl)ethanone (3e): ^{1}H NMR (400 MHz, $CDCl_3$) d 3.89 (s, 3H), 4.45 (s, 2H) 6.93-6.98 (m, 2H), 7.92-7.95 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) d 30.18, 56.44, 113.15, 127.74, 132.16, 162.84, 189.54, HRMS (ESI) *m/z* 227.9788, calc. for $C_9H_9O_2Br$ 227.9791.

2-Bromo-1-(4-fluorophenyl)ethanone (3f): ^{1}H NMR (400 MHz, $CDCl_3$) d 4.43 (s, 2H), 7.14-7.19 (m, 2H), 8.00-8.13 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) d 30.53,115.05, 115.81, 128.80, 129.82, 131.23, 131.45, 163.44, 167.48,189.68. ^{19}F NMR (376 MHz, $CDCl_3$) d 102.59. HRMS (ESI) *m/z* 215.9587, calc. for C_8H_6OBrF 215.9589.

2-Bromo-1-(3-hydroxyphenyl)ethanone (3g): ^{1}H NMR (400 MHz, $CDCl_3$) d 4.46 (s, 2H), 6.14 (s, 1H), 7.14-7.17 (m, 1H), 7.37-7.38 (m, 1H), 7.56-7.58 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) d 30.88, 113.93, 121.17, 122.92, 130.45, 136.73, 156.41, 190.77. HRMS (ESI) *m/z* 213.9631, calc. for $C_8H_7O_2Br$ 213.9633.

2-Bromo-1-(4-methylphenyl)ethanone (3h): m.p. 38-39 ºC; lit. 38-40 ºC [32]; ^{1}H NMR (400 MHz, $CDCl_3$) d 2.13 (s, 3H), 4.43 (s, 2H) 6.94-6.99 (m, 2H), 7.93-7.96 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) d 30.21,46.15, 113.85, 127.77, 132.25, 157.54, 188.10; HRMS (ESI) *m/z* 211.9788, calc. for $C_9H_9O_2Br$ 211.9785.

RESULTS AND DISCUSSION

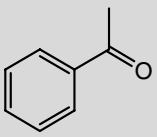
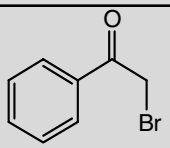
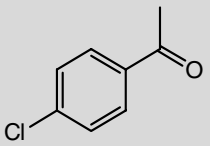
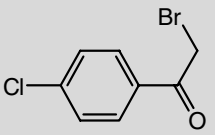
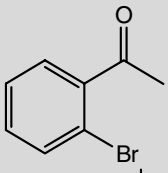
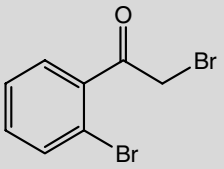
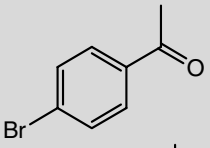
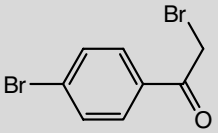
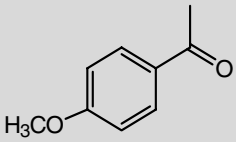
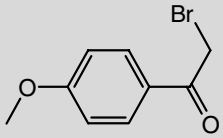
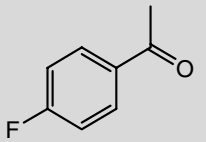
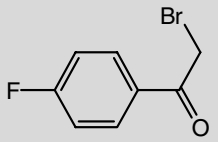
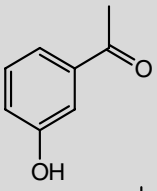
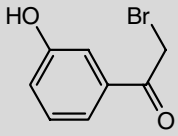
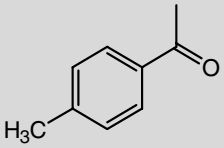
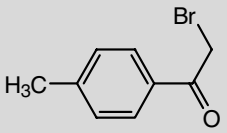
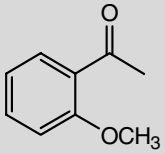
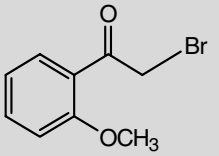
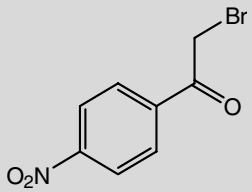
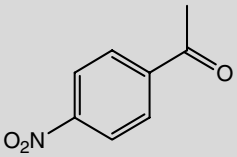
As a part of our growing interest in ultrasound promoted one-pot synthesis of heterocyclic compounds, α-halo ketones is the key precursor used in synthesis of most of the biologically and pharmacologically important heterocyclic compounds. It prompted our interest to design new methods for the synthesis of α-bromo ketones under environmentally benign conditions. N-Bromosuccinimide is selected as a brominating agents for the selective mono-bromination of various acetophenones .The synthesis was carried out by mixing equimolar quantities of acetophenone (1), N-bromosuccinimide (2) under ultrasonic irradiation at 18 to 25 kHz and a power of 300 W in different solvents. In order to search for the better solvent, the ultrasonic assisted reaction to obtain compound **3a** was examined using different solvents *viz*. water, PEG-400, methanol, dichloromethane, DMF and ethanol. The results are summarized in Table-1. Although the reaction could be efficiently carried out in all these solvents, the use of water and PEG-400 in different proportion consistently slightly higher yields and shorter reaction times (entry 2). It was observed that an increase in the frequency from 18 kHz to 25 kHz causes a very slight increase in yields. Therefore, we have followed ultrasonic irradiation at 25 kHz. By using this frequency, products (**3a-3j**) were obtained in high yields and significantly shorter reaction times (Table-2). The electronic effect and the nature of substituent on the aromatic ring of acetophenones shows slight effect in terms of yields, under the same reaction conditions. Aromatic ketones bearing electron withdrawing groups (such as nitro group) in *meta*- and *para*- positions slightly but consistently increased the yield.

TABLE-1
OPTIMIZATION OF REACTION CONDITION

Entry	Solvents	Reaction time (min)	Frequency (kHz)	Yield (%)
1	Water	18	25	85
2	PEG-400	17	25	84
3	Water and PEG-400 (2:1)	16	25	87-94
4	Di-chloro methane	23	25	76
5	Methanol	20	25	73
6	Ethanol	23	25	67
7	DMF	22	25	52
8	DMSO	25	25	63

[a]Isolated yield

TABLE-2
ULTRASOUND MEDIATED SYNTHESIS OF PHENACYL BROMIDES

Entry	Acetophenones	Product	Time (min)	Yield (%)
3a			17	87
3b			15	91
3c			16	89
3d			16	88
3e			15	90
3f			15	94
3g			16	86
3h			19	85
3i			16	89
3j			15	93

[a]Reaction condition: 1) acetophenones (0.5 mmol), NBS (0.5 mmol), (PEG-400/water in (1:2) ratio (5 mL) at 80 °C at 300 W; frequency 25 kHz; [b]Isolated yield.

Conclusion

In conclusion, a novel and environmentally benign approach for the synthesis of α-bromo aromatic ketones using N-bromo-succinimide as brominating agent by using ultrasound waves in PEG-400 and water (1:2) as reaction medium is reported. The important features of this procedure are enhanced reaction rate, mild reaction condition, high yields and green chemistry such as avoiding hazardous organic solvents, use of toxic catalysts and waste, ease of work up procedure and high yield.

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